bulges, loops, and hairpins, which contain single-stranded regions of RNA. No new matter has been added.

New claim 31 incorporates elements of existing claims 21 and 26. No new matter has been added.

Applicants have amended the specification, as requested by the Examiner, to delete hyperlinks and other forms of browser-executable code. Applicants have also amended the specification to correct typographical errors and to delete a section that was duplicative of page 45, line 27 through page 61, line 27.

Applicants have also amended the specification to incorporate material deemed essential by the Examiner and allegedly inappropriately incorporated by reference. This amendment is accompanied by an affidavit executed by Dr. David Ecker stating that the amendatory material consists of the same material that was deemed by the Examiner to be essential and incorporated by reference.

I. The Claimed Invention Is Not Anticipated

Claims 1-3, 17, 18, 21-23 and 26-28 stand rejected under 35 U.S.C. §102(a) as allegedly being unpatentable over Chen *et al.*, *Biochemistry*, **1997**, *36*, 11402-11407 (hereinafter, the "Chen reference"). Applicants traverse the rejection and respectfully request reconsideration thereof since the Chen reference fails to teach each and every element recited in the rejected claims.

The Chen reference reports structure-based discovery of ligands that are targeted to double stranded RNA. In particular, the Chen reference reports that a series of lead compounds was generated through a database search for ligands with shape complementarity to the RNA deep major groove. The RNA molecule reported in the Chen reference is entirely complementary with itself, thus having a complete double helical structure with no regions of single stranded RNA. Of more than 400 compounds that were examined graphically and found to fit well into the deep major groove, only 11 compounds were selected for testing. In order to determine the binding site of one of the compounds, lividomycin, ^{19}F-NMR solvent isotope shift measurements were carried out on RNA duplexes containing 5-fluorouracil (FU) (see, page 11405, first column). The Chen reference

reports that when FU is incorporated into nucleic acid duplexes, the fluorine atom lies in the major groove providing a probe for binding interactions in that groove. The presence of a tightly bound ligand in the major groove should limit the solvent exposure of the major groove atoms and thereby decrease or eliminate the solvent isotope shift.

A prior art reference anticipates a claim if each and every element of the claim appears in the prior art reference. *See C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1349, 48 U.S.P.Q.2d 1225, 1230 (Fed. Cir. 1998). Applicants respectfully submit that the Chen reference does not disclose every element of the rejected claims.

Claims 1-3 and 21-23 of the invention recite that a molecular interaction site on the target RNA molecule is identified and a three dimensional representation of the site is compared to a virtual library of compounds. In addition, claims 17 and 18 recite a molecular interaction site within RNA. The Chen reference does not teach a molecular interaction site on a target RNA molecule let alone identification of a molecular interaction site on a target RNA molecule prior to comparing a three dimensional representation of the same to a virtual library of compounds. The specification defines molecular interaction sites as "small, usually less than 30 nucleotides, independently folded, functional subdomains contained within a larger RNA molecule." *See*, for example, page 16, lines 1-2 of the specification. The Chen reference does not teach identification of a small, independently folded, functional subdomain contained within a target RNA molecule. Rather, the Chen reference reports the use of r(UAAGGAGGUGAU)·r(AUCACCUCCUUA), an RNA duplex for which a crystal structure is available, as a target RNA molecule. The molecular "target site," according to the terminology of the Chen reference, of this duplex was "focused on the central region of base pairs 4-9 in the major groove." *See* page 11402 of the Chen reference. Thus, the Chen reference obtained an RNA duplex that had recently been crystalized and focused their ligand binding studies on the major groove of the central portion of the duplex. In contrast, Chen reference does not teach that their "target site" is independently folded and also does not disclose that the site is a functional subdomain of their target RNA molecule. Rather, the Chen reference simply used the *major groove* of a central portion of their target RNA molecule as their target site. The major groove of the central six base-pair region of a twelve base-pair RNA duplex is not independently folded and is not a

functional subdomain of the duplex. Thus, the Chen reference does not teach identification of a molecular interaction site on their target nucleic acid duplex.

In addition, at no time does the Chen reference teach that steps that were taken to identify a small, independently folded subdomain of their target molecule. Further, the Chen reference makes no reference whatsoever to the identification of an independently folded "target site." Rather, the Chen reference simply states that they focused their ligand binding studies on the major groove of the central portion of their target RNA molecule. Indeed, the Chen reference does not describe any sort of analysis or experimentation to determine whether their target RNA duplex contained an independently folded functional subdomain or determine where that subdomain might be located. Thus, Chen reference does not identify a small, independently folded molecular interaction site on their target RNA molecule. Therefore, the Chen reference does not teach each and every element of claims 1-3, 17, 18 and 21-23.

Claims 26-28 recite, *inter alia*, "identifying at least one molecular interaction site on said target RNA by comparing the nucleotide sequence of said target RNA with the nucleotide sequence of a RNA from a different taxonomic species, identifying at least one conserved region, determining the secondary structure of said conserved region." Nowhere does the Chen reference teach identification of a molecular interaction site, let alone teach the steps recited in claims 26-28. Thus, the Chen reference does not teach each and every element of claims 26-28.

In view of the foregoing, Applicants respectfully request that rejection of claims 1-3, 17, 18, 21-23 and 26-28 under 35 U.S.C. §102(a) be withdrawn.

II. The Claims Are Enabled

Claims 1-5 and 17-30 stand rejected under 35 U.S.C. §112, first paragraph because the specification allegedly does not reasonably enable the general discovery of molecular interaction sites in macromolecules. Applicants traverse the rejection and respectfully request reconsideration thereof because one skilled in the art would be able to practice the claimed invention without being required to perform undue experimentation.

The Office Action states that modeling software that allows three dimensional

representations of molecular interaction sites to be produced from two dimensional nucleotide sequences is necessary in order to fully enable the invention, and therefore may not be incorporated by reference. Applicants have amended the specification, as suggested in the Office Action, to incorporate the names of specific software modeling packages made available by the companies recited in the specification at page 94, lines 29-31, which can be used to produce three dimensional representations of molecular interaction sites. Applicants respectfully submit that, in light of the amendments to the specification incorporating the names of specific software modeling packages useful in the invention, the specification enables the skilled artisan to make and use the claimed invention without undue experimentation. Applicants have disclosed means, other than the use of DOCK software, for computer modeling of molecular interaction sites. The specification is commensurate in scope with the claims because the specification teaches the skilled artisan several different means for producing three dimensional representations of two-dimensional molecular interaction sites. The skilled artisan would not have to engage in undue experimentation in order to produce a three dimensional representation of a molecular interaction site from a two-dimensional nucleotide sequence. Accordingly, Applicants respectfully request that the rejection under §112, first paragraph be withdrawn.

III. Conclusion

In view of the foregoing, Applicants submit that the claims as amended are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,

Paul K. Legaard
Registration No. 38,534

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Enclosure: Declaration of Dr. David J. Ecker

WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439